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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

ROARK, JESSICA H

ART UNIT	PAPER NUMBER
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1644

33

DATE MAILED: 02/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/424,705

Applicant(s)

LITTLE ET AL.

Examiner

Jessica H. Roark

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 18 September 2002 and 10 December 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,4-7,9,12-14,18-21 and 23-27 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.

- 6) ☒ Claim(s) 1,2,4-7,9,12-14,18-21 and 23-27 is/are rejected.

- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.

- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 September 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☒ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

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## RESPONSE TO APPLICANT'S AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection on 12/10/02. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/18/02 has been entered.
2. Applicant's amendments, filed 9/18/02 and 12/10/02 (Paper Nos. 22 and 30), have been entered. Claims 3, 8, 15-17 and 22 have been cancelled.  
Claims 10-11 have been cancelled previously.  
Claims 1-2, 4-7 and 9 have been amended.  
Claims 1-2, 4-7, 9, 12-14, 18-21 and 23-27 are pending and under consideration in the instant application.
3. This Office Action will be in response to applicant's arguments, filed 9/18/02 (Paper No. 22). The rejections of record can be found in a previous Office Action (Paper Nos. 13, 19 and 27).  
It is noted that New Grounds of Rejection are set forth herein.

### *Drawings*

4. The Formal Drawings filed 9/18/2002 have been found acceptable by the Draftsman.

### *Priority*

5. Receipt is again acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

A certified translation of DE 197 21 700.1 was filed on 12/10/02 and appears to provide adequate written support for the instant claim limitations.

### *Sequence Compliance*

6. Sequence compliance: Applicant's provision of a new CRF, Sequence Listing, and Statement that the contents are identical on 12/10/02 (Paper No. 30), is acknowledged. The CRF has been found acceptable and entered. However, Applicant is required to identify the sequences with SEQ. ID NOS wherever sequences occur in the specification, drawings, and claims, in order to full satisfy the requirements of 37 CFR 1.821 (d) (see also MPEP 2422.02-2422.03).

In particular, Applicant's attention is called to the Brief Description of Figures 3A and 3B, which as amended 9/18/02 lack sequence identifiers.

***Objections to the Specification***

7. The previous objection to the specification for failure to comply with the requirements of 37 CFR 1.77 is withdrawn in view of Applicant's amendment, filed 9/18/02, providing Section Headings.

***Claim Objections***

8. The previous objection to claim 5 under 37 CFR 1.821(d) for failing to recite sequence identifiers is withdrawn in view of the amendment filed 9/18/02 and the Hawkins-type Declaration provided by Applicant on 9/18/02. It is noted that page 2 at the last paragraph provides the various primers by name and notes the references providing the primer sequences. Therefore the amendment filed 9/18/02 introducing the primer sequence via incorporation by reference does not appear to introduce New Matter into the specification.

9. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

It is noted that the amendment filed 9/18/02 limits the recombinant antibody product of claim 1 to one comprising the amino acid sequence depicted by SEQ ID NO:2. SEQ ID NO:2 depicts the polar amino acid as serine, therefore claim 2 fails to further limit claim 1.

10. Claim 18 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 9. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Claim Rejections - 35 USC § 112 second paragraph***

11. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

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12. Applicant's amendment, filed 9/18/02, has obviated the previous rejections of claims 2, 5, 8, 12-13, 15-17, 19 and 22 under 35 U.S.C. 112, second paragraph.

13. Claims 4-7, 9, 12-14 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim steps 4b-4d, and dependent claims 5-7, 9, 12-14 and 18-21, recite the limitation "the DNA". However, there is insufficient antecedent basis for this limitation in these claims because step (a) of claim 4 recites a cDNA, not a DNA.

B) Claims 4-6, 9, 12 and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step that results in the serine found at position H100A of the product set forth in claims 1 and 2.

It is noted that step 4c only results in substitution with "a polar amino acid".

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

***Claim Rejections - 35 USC § 112 first paragraph***

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

15. Applicant's amendment, filed 9/18/02, has obviated the previous rejection of claims 8, 15-17 and 22 under 35 U.S.C. 112, first paragraph, enablement.

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16. Claims 1-2, 4-7, 9, 12-14, 18-21 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed. *This is a New Matter rejection for the following reasons:*

Applicant's amendment, filed 12/20/01, introduced the claim language "a recombinant antibody product" and pointed to support on page 2 at lines 9-14 of the specification as filed. However, after further review this claim language does not appear to be supported in the specification as filed.

In particular, the specification discloses only recombinant antibody products that are the scFv antibody set forth in SEQ ID NO:2 and the bispecific antibody set forth in SEQ ID NOS: 4 and 6. The term "a recombinant antibody product" encompasses *any* antibody produced by recombinant means, and thus is an extensive genus encompassing chimeric and other forms of antibodies so long as they are "recombinant". The specification does not appear to clearly contemplate a genus encompassing a recombinant antibody product as currently recited. The disclosure of two species of recombinant antibody products does not appear to provide an adequate written description to support a claim to the broader genus of any recombinant antibody product.

Thus the specification does not appear to provide an adequate written description of "a recombinant antibody product". The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

*Applicant is required to cancel the New Matter in the response to this Office Action.*

Alternatively, Applicant is invited to clearly point out adequate written support for the instant limitation.

### ***Claim Rejections – 35 U.S.C. §§ 102 and 103***

17. Applicant has previously asserted in the amendment filed 12/20/01 that the claims are entitled to a priority date of May 23, 1997. A certified translation of foreign priority document DE 197 12 700.1 was provided on 12/10/02 which appears to show adequate written support for the instant claims.

Thus Kipriyanov et al. (Protein Engineering April 1997 [dispatched June 2, 1997]; 10:445-453, IDS #5) is not available as a reference under 35 USC 102(a).

18. The previous rejection of claims 1-9, 12-25 and 27 under 35 U.S.C. 102(a) as being anticipated by Kipriyanov et al. (Protein Engineering April 1997 [dispatched June 2, 1997]; 10:445-453, IDS #5) in Paper No. 19 is withdrawn.

19. Similarly, the previous rejection of claim 26 under 35 U.S.C. 103(a) as being unpatentable over Kipriyanov et al. (Protein Engineering April 1997 [dispatched June 2, 1997]; 10:445-453, IDS #5) and Nitta et al. (The LANCET 1990; 335:368-371, IDS #9) is withdrawn.

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20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1-2, 4-6, 9, 12, 18-20, 23-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroon et al. (Pharmaceutical Res. 9:1386-1393 1992, of record) in view of Senoo et al (US Pat. No. 5,852,177, of record) and Kipriyanov et al. (J. Immunol. Meth. 1996; 196:51-62, IDS #4).

Applicant's argument, filed 9/18/02, have been fully considered but have not been found convincing.

Applicant's arguments are addressed below in the context of the rejection of record as modified to address the newly added claim limitations.

The instant claims are drawn to a recombinant antibody product comprising the amino acid sequence depicted by SEQ ID NO:2, which depicts a scFv form of the heavy and light chains of the OKT3 antibody (CRL 8001) in which the cysteine at position H100A has been exchanged with the polar amino acid serine. The claims are also drawn to a method of producing this antibody.

Kroon et al. review the art-recognized therapeutic applications of the OKT3 antibody and the art-recognized problems associated with long term storage of the OKT3 antibody (e.g., "Introduction" on page 1386). Kroon et al. teach that the OKT3 antibody is inactivated while in storage as a consequence of formation of cross-links between heavy chain in the region of amino acids 99-121 (see entire document; especially page 1391-1392 bridging paragraph and the sequence of Figure 1). Although the numbering system used is different, Kroon et al. teach that the Cys in the third heavy chain CDR (i.e., CDR3) *is a likely candidate* for oxidation which would lead to degradative structural changes for OKT3 (see especially page 1390). Kroon et al. clearly indicate on page 1390 that "[t]he most significant change in the peptide maps of OKT3 with long term storage was a decrease in the size of the peak corresponding to H99-121" and that "there is a non-disulfide-bonded Cys at residue 105, a likely candidate for oxidation."

Kroon et al. further teach that using site directed mutagenesis to synthesize more stable analogues would be beneficial for the development of therapeutics (e.g., page 1392, last paragraph).

Thus Kroon et al. provide guidance to replace the heavy chain CDR3 cysteine which decreases OKT3 stability and is the same cysteine as that at position H100A using the instant numbering system. Kroon et al. further teach the application of site-directed mutagenesis as a method of replacing the cysteine and generating more stable forms of OKT3.

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Consequently, one of ordinary skill in the art at the time the invention was made, armed with the teachings of Kroon et al., would have been motivated to change the cysteine at position H100A (Kabat numbering system) in CDR3 of the OKT3 heavy chain by site-directed mutagenesis.

Kroon et al. do not teach that the cysteine at position H100A of the OKT3 antibody should be replaced with the polar amino acid serine.

However, Senoo et al. teach that formation of intra and interchain disulfide bonds is detrimental to protein stability (see entire document, especially column 1 to column 2, bridging paragraph) and that the conversion of a cysteine to serine eliminates this problem and improves protein stability (e.g., column 7, lines 55-57).

Thus the ordinary artisan at the time the invention was made would have been motivated to select serine in particular as the amino acid to replace the cysteine at H100A in mutagenesis of the OKT3 antibody.

Kroon et al. also do not teach a detailed method of producing a recombinant antibody product in which the cysteine at position H100A of the OKT3 antibody has been exchanged with the polar amino acid serine, nor do they produce OKT3 having the cysteine at H100A changed to a serine. Neither do Kroon et al. teach the amino acid sequence depicted in SEQ ID NO:2.

Kipriyanov et al. teach a method of producing scFv from hybridomas of interest by obtaining mRNA, transcribing the mRNA to cDNA, amplifying the heavy and light chain variable regions using the primers Bi5, Bi8, Bi4, and Bi3f (i.e., SEQ ID NOS: 8-11), cloning the amplified DNA into the pCR-Skript SK(+) vector adapted for site-specific mutagenesis, insertion of the DNA into the expression vector pHOG21, and finally expression of the scFv using E. Coli XL1-Blue (see entire document, especially sections 2.2 to 2.5).

The pHOG21 vector taught by Kipriyanov et al. results in the insertion of a pelB leader sequence at the amino terminus of the cloned heavy chain variable region, the insertion of a linker sequence comprising the YOL epitope between the heavy and light chain variable region sequences and the insertion of a tandemly linked c-myc and 6-His tag at the carboxy terminus of the cloned light chain variable region (see in particular figure 2 on page 57).

Kipriyanov et al. review the art-recognized advantages of the scFv form of an antibody at the bridging paragraph of pages 51-52. Kipriyanov et al. further teach that their particular cloning approach is advantageous because the 6-His tag could be used in a rapid single-step purification of the scFv antibody (e.g., Section 3.2 on page 57, and comments on page 52, final full paragraph), and an antibody to the C-terminal c-myc tag could be used to enrich for clones containing the correct insert (e.g., Section 3.4 on page 59, and comments on page 52, final full paragraph).

Thus Kipriyanov et al. teach the desirability of the scFv form of therapeutic antibodies and an advantageous method of producing such antibodies.

Kipriyanov et al. also demonstrate that this scFv cloning method could be successfully applied to the OKT3 antibody, because Kipriyanov et al. teach on page 57 in the right column that the an anti-CD3 scFv-dmOKT3 antibody was produced by them and that this scFv antibody still bound its CD3 antigen.



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Therefore it would have been obvious to one of ordinary skill in the art to modify the method of Kipriyanov et al. to include the introduction of a mutation in which heavy chain cysteine H100A (in the instant numbering system) of the OKT3 antibody (CRL 8001) was replaced with serine in order to obtain a more stable OKT3 antibody. Site-directed mutagenesis to produce such a molecule was well within the skill of the ordinary artisan at the time the invention was made. Primer selection and design for the mutagenesis would have been a matter of selection based upon the sequence to be mutated and the change introduced. Kroon et al. give clear direction to H100A, which is the Cys found in the third CDR of the OKT3 heavy chain. Kipriyanov et al. teach the heavy and light chain primers, cloning vector and expression system for producing a scFv form of OKT3 and show not only that a scFv of OKT3 can be produced, but that it is functional (i.e., still binds CD3). Senoo et al. teach that mutagenesis to Ser eliminates disulfide bonding detrimental to stability. Given the teachings of these references, the ordinary artisan would have had a reasonable expectation of producing a mutated OKT3 scFv in which the Cys in CDR3 (H100A) had been exchanged for cysteine using a modification of the method of Kipriyanov that included site-directed mutagenesis.

As set forth supra, Kroon et al. provide clear motivation for producing an OKT3 antibody in which the Cys in CDR3 of the heavy chain was mutated in order to improve the stability of the therapeutic OKT3 antibody; and the teachings of Senoo et al. provide motivation for selection of Ser as the replacement amino acid.

Applicant has argued in the response filed 9/18/02 that the references neither alone or in combination teach or suggest the amino acid sequence of SEQ ID NO:2, now recited in the instant claims.

SEQ ID NO:2 sets forth the amino acid sequence of a scFv form of the OKT3 antibody in which the Cys found in heavy chain CDR3 has been replaced by a Ser.

SEQ ID NO:2 is comprised, from the amino to carboxy terminus, of:

- a) a pelB leader sequence, as set forth in Figure 2A of Kipriyanov et al.;
- b) the OKT3 VH bearing the Cys to Ser replacement;
- c) a linker sequence that is the linker sequence set forth in Figure 2B of Kipriyanov et al.;
- d) the OKT3 VL;
- e) a c-myc tag sequence, as set forth in Figure 2C of Kipriyanov et al.; and
- f) a 6 His tag, as set forth in Figure 2C of Kipriyanov et al.

Components (a), (c), (e) and (f) are derived from the pHOG21 expression vector taught by Kipriyanov et al. As taught by Kipriyanov et al., an antibody VH and VL can be inserted into the pHOG21 vector sequence by amplifying the cDNA of the antibody with the primers provided in Table 1 of Kipriyanov et al. The primers taught by Kipriyanov et al. result in restriction sites that allow insertion of the antibody VH and VL sequences such that defined portions of the VH and VL chains are inserted (i.e., the primers define the fragment of the VH and VL chains inserted into the expression vector).

The amino acid sequence of the OKT3 antibody VH and VL chains is an intrinsic property of the antibody. The non-vector sequence of SEQ ID NO:2 appears to differ from that of the OKT3/CRL8001 amino acid sequence only by virtue of the Cys to Ser replacement (for which motivation to make the change exists), and by the amino and carboxy termini. However, the amino and carboxy termini are necessarily defined by the heavy and light chain primers used to amplify the heavy and light chain variable regions and the primers taught by Kipriyanov et al. necessarily result in the OKT3 VH and VL amino acid sequence components of SEQ ID NO:2.

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Thus contrary to Applicant's assertions, the teachings of the combination of the references do appear to result in the amino acid sequence set forth in SEQ ID NO:2. Applicant has provided insufficient evidence that the amino acid sequence that results from the production of a scFv form of OKT3 using the method of Kipriyanov et al. and adding an additional step to introduce the Cys to Ser replacement mutation, as suggested by the teachings of Kroon et al. and Senoo et al., differs from instant SEQ ID NO:2. The burden is on the applicant to establish a patentable distinction between the claimed and referenced antibody/methods.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is maintained as applied to the amended claims.

22. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kroon et al. (Pharmaceutical Res. 9:1386-1393 1992, of record) in view of Senoo et al (US Pat. No. 5,852,177, of record) and Kipriyanov et al. (J. Immunol. Meth. 1996; 196:51-62, IDS #4) as applied to claims 1-2, 4-6, 9, 12, 18-20, 23-25 and 27 above, and in further view of Nitta et al. (The LANCET 1990; 335:368-371, IDS #9).

The claims are drawn to a bispecific antibody comprising the amino acid sequence depicted by SEQ ID NO:2.

Kroon et al. in view of Senoo et al. and Kipriyanov et al. have been discussed supra.

Kroon et al. in view of Senoo et al. and Kipriyanov et al. do not teach a bispecific antibody comprising SEQ ID NO:2.

Nitta et al. teach a bispecific antibody comprising the anti-CD3 monoclonal antibody OKT3 and how to make it (see entire document, e.g., Abstract and "Preparation of bispecific antibody" on page 368). Nitta et al. also teach the in vitro use of the bispecific antibody comprising OKT3 in the production of LAK cells which were used in adoptive transfer experiments to successfully target glioma cells in patients and were found to be more effective than LAK cells generated without the OKT3 bispecific antibody present (see entire document, as summarized in Abstract).

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to substitute the more stable form of the OKT3 antibody taught by the combination of Kroon et al. Senoo et al. and Kipriyanov et al. for the unmutated antibody used in the bispecific construct of Nitta et al. in order to obtain a more stable bispecific antibody for use in in vitro generation of anti-tumor LAK cells. The ordinary artisan at the time the invention was made would have been motivated to make the substitution in order to produce a more stable antibody form of the therapeutic OKT3 antibody, which the ordinary artisan would have recognized as more desirable for use in the methods of Nitta et al. Given the teachings of the references, the ordinary artisan would have had a reasonable expectation of successfully producing a bispecific antibody comprising SEQ ID NO:2. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

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**Conclusion**

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.  
Patent Examiner  
Technology Center 1600  
February 20, 2003

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